

REMARKS

Claims 1-6, 8-12, 17, and 19-36 are pending in this application. Claims 19-36 have been withdrawn from further consideration as being drawn to nonelected subject matter. Claims 1-6, 8-12, and 17 were rejected under 35 U.S.C. § 112, first paragraph. Claim 17 was rejected under 35 U.S.C. § 112, second paragraph.

By this amendment, claims 4, 8 and 17 have been canceled, claims 1, 5, and 9-11 have been amended, and new claim 44 has been added without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification and support for new claim 44 is found, *inter alia*, at page 12, lines 9-11.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-6, 8-12, and 17 were rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner points out that the specification clearly asserts that the utility of the invention is to alleviate a symptom of schizophrenia and that enablement is evaluated in view of the

asserted utility. The Examiner further states that the “asserted utility of alleviating a symptom of schizophrenia is accepted as a credible utility, albeit one that is not enabled by the instant specification.” Office Action, page 3.

According to the Office, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. §112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider obvious. M.P.E.P. §2164.08. The fact that the experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. M.P.E.P. §2164.01.

The rejection is essentially related to the effective “scope” of the enablement regarding several aspects of the claimed invention. For example, the Examiner states that the “claims are very broad in scope, covering the use of any cell type, as well as wide variety of combinations of cell type and support matrix” and then concludes that “it is left up to the skilled artisan to come up with a combination that produces a therapeutic effect.” Office Action, page 3.

Applicants respectfully disagree with this conclusion for reasons already of record and Applicants maintain that use of “cells which produce dopamine or a dopamine precursor” is fully enabled by the specification in view of the understanding in the art. Be that as it may and solely to expedite prosecution of this case, the claims have herein been amended to recite a particular set of cells which produce dopamine or a dopamine precursor and to recite support matrix made of particular materials. These amendments are intended to eliminate some of the Examiner’s articulated concerns regarding enablement of the claim scope.

The cells and the support matrix materials of the cell/support complex now claimed are described in the specification and well known in the art at the time the application was filed as

effective in providing dopamine or a dopamine precursor upon implantation into a brain. In addition to the specification disclosure, Applicants respectfully point out that many of the references of record demonstrate that administration of cell/support complexes as claimed provide dopamine or a dopamine precursor in amounts effective to ameliorate symptoms associated with dopamine deficiency.¹ Thus, Applicants respectfully submit that the level of skill in the art is high and that the skilled artisan would be able to make and use the cell/support complex as claimed without undue experimentation.

In support of this rejection, the Examiner states that “[a]t present, the effect of dopamine replenishment within the prefrontal cortex of a diseased brain is unknown.” Applicants respectfully disagree with this statement.

Dopamine deficiency in the prefrontal cortex is associated with symptoms of schizophrenia such as negative symptoms and cognitive deficits. The specification describes that cognitive defects associated with schizophrenia include deficits in working memory and visuospatial memory. This is also described in references of record. For example, the review article of Abi-Dargham et al. describes the association of a deficit in prefrontal dopamine function and schizophrenia and the association of deficits in delayed-response tasks observed in nonhuman primate models of prefrontal dopamine deficiency.² In this discussion, the authors cite to earlier references in the art³ as showing the relationship between prefrontal dopamine deficiency and cognitive function deficit. For example, Brozoski et al. (1979) demonstrated that 6-hydroxydopamine (6-OHDA) lesions in the dorsolateral prefrontal cortex in pretrained rhesus monkeys produced impairments in performance on the spatial delayed response task. This study

¹ See, for example, U.S. Patent No. 5,618,531, Potter et al. (1997), Subramanian et al. (two references from 1998), Subramanian et al. (1999), all of record. See also Watts et al. (2003), submitted herewith.

² See, for example, page 413, Abi-Dargham et al. (2003), of record.

³ The review article cites references such as Brozoski et al. (1979, *Science* 205:929-932), Arnsten et al. (1994, *J. Psychopharmacol.* 11:151-162) and Cai et al. (1997, *J. Pharmacol. Exp. Ther.* 283:183-189).

then showed that acute administration of L-dopa (levodopa) reinstated spatial working memory performance in the monkeys, thus demonstrating the critical role for dopamine in this cognitive process.

In another primate model, the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) used to model symptoms of Parkinson's Disease also induces cognitive deficits as shown in Fernandez-Ruiz et al (1999).⁴ This study shows that dopamine replacement therapy, in the form of levodopa (L-dopa), significantly improved memory impairments and spatial delayed response tasks, i.e., prefrontal cortex dependent activities.

Thus, at the time of filing, dopamine replenishment therapy was known to ameliorate symptoms of prefrontal cortex dysfunction or disease.

The specification describes that cognitive defects associated with schizophrenia are ameliorated through administration of the cell/support complex as claimed to the prefrontal cortex of the subject.

As discussed above, administration of dopamine or a dopamine precursor to a brain through implantation of a cell/support complex as claimed is described in the specification and is well known in the art. Submitted herewith is a recent review article by Watts et al. which compiles and summarizes some of the work already of record. As with the references of record⁵, this article demonstrates that the cell/support complex implanted in a specific dopamine deficient regions of the brain (in this case, animal models and Parkinson's disease patients) ameliorates the symptoms associated with dopamine deficiency in the region.

The specification in combination with that known in the art enables the skilled artisan to make and use the invention as claimed. Thus, the pending claims are in compliance with the

⁴ Fernandez-Ruiz et al. (1999) *Psychopharmacology* 147:104-107, submitted herewith.

⁵ For example, U.S. Patent No. 5,618,531, Potter et al. (1997), Subramanian et al. (two references from 1998), Subramanian et al. (1999).

enablement requirements. Applicants respectfully submit that the specification provides a reasonable amount of guidance to the skilled artisan with respect to the direction in which the experimentation should proceed to optimize the teachings of the specification and the art and that any additional necessary experimentation is presumed to be within the level of ordinary skill in the art and thus, not undue. Varying the cell/support complex, for example in dosage, cell type or matrix material, to achieve a lessening of a symptom is well within the bounds of experimentation by one of skill in the art in view of the teaching in the specification.

Thus, Applicant respectfully submits that a *prima facie* case of lack of enablement has not been established.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claim 17 was rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In order to expedite prosecution of this case, claim 17 has herein been canceled rendering the rejection moot. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000600.

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Respectfully submitted,

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